#30 L.P 3-11-96

Docket No. 9425/46701

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Inventor: Samuel BOGOCH

Serial No.: 08/031,562

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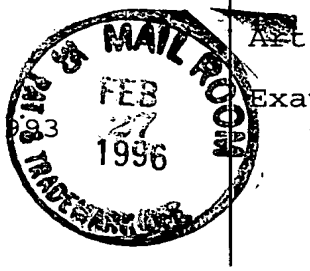
For: RECOGNIN VACCINES



Art Unit: 1813

Examiner: J. Krsek-Staples

Commissioner of Patents
and Trademarks
Washington D.C. 20231

REPLY BRIEF UNDER 37 C.F.R. § 1.193

Sir:

This is Appellant's Reply Brief under 37 C.F.R. §1.193(b) pursuant to the Examiner's Answer mailed December 27, 1995. This Reply is taken with respect to new points of argument and new grounds of rejection raised in the Examiner's Answer.

The Examiner states that the Brief includes a statement that the finally rejected claims do not stand or fall together but fails to present reasons in support thereof.

Appellant respectfully disagrees.

In section (7), at pages 4 through 5 of Appellant's Brief under 37 C.F.R. § 1.192, filed October 5, 1995, it is stated that claim 1 constitutes a first group and claim 2 constitutes a second group. In section (8), the argument in rebuttal of the rejections of claims 1 and 2 is broken down into two sections, each section directed to either claim 1 or claim 2.

It is submitted in section (8) that the process set forth in claim 1 is fully enabled by the specification, in that the steps necessary to carry out the claimed process for inhibiting the

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growth of or destroying cancer cells in a patient are clealy taught throughout the specification. In regard to claim 2, it is further and separately argued that the specification provides an enabling disclosure to the skilled practioner to make and use the claimed vaccine. It is pointed out in the section of the Argument directed to the enablement of claim 2 that details concerning the synthesis of the claimed vaccine are provided in Appellant's co-pending application Serial No. 07/744,649. These details, however, are merely supplemental to the disclosure of the present specification and are not relied upon as essential to the disclosure of the claimed invention, contrary to the Examiner's assertion at page 8 of the Examiner's Answer.

It is respectfully submitted that by setting forth each of these separately argued points, Appellant has set forth reasons why the separately argued claims are patentable, thus meeting the obligations to set forth the patentability of each group of claims separately as set forth by 37 C.F.R. §1.192(c)(7). It is submitted that the Examiner's conclusion that no reasons were set forth in support of Appellant's groupings of the claims is in error. It is, therefore, submitted that the Honorable Board of Patent Appeals and Interferences should consider the patentability of claim 1 and claim 2 separately.

New Grounds of Rejection

In the Examiner's Answer, the Examiner raises a new ground of rejection under 35 U.S.C. §112, second paragraph. The Examiner asserts that the meaning of the phrase "immunological specificity" is unclear. The Examiner also states that it is unclear whether Recognin-L, Recognin-M and recognin generate identical antibodies. The Examiner concludes, therefore, that the specification fails to adequately teach how to make and/or use the invention.

This new ground of rejection is respectfully traversed as follows.

Turning first to the meaning of the phrase "immunological specificity", it is respecfully submitted that the skilled practitioner in the field of immunology would understand the meaning of this phrase as an art accepted term to mean that the claimed vaccine product is cross-reactive with antibodies which recognize and interact with Recognin. Moreover, in the present case, the skilled practitioner would recognize the use of this art-accepted terminology to mean that the vaccine product recognizes the antigenic epitope common to malignin, Recognin-L and Recognin-M, since the antibodies generated by any of the three are indistinguishable from one another. As noted by the Examiner, the terms "Recognin" and "malignin" are used interchangeably. All Recognins react with the same anti-Recognin/anti-malignin antibodies. Thus, the use of this art accepted phrase to describe the properties of the vaccine product is not vague and indefinite.

The Examiner states that it would require undue experimentation to identify other Recognins and to determine whether these antigens would be effective in the treatment of cancer. However, the data set forth at pages 5 and 6 of the specification clearly show that all types of cancer cells tested, i.e., brain cancer cells, breast cancer cells and P3J lymphoma cells, produce the same, or at the very least, antigenically similar Recognin and each Recognin produces the same antibody. Furthermore, the antibody recognizes all three types of cancer cells as well as other common cancer cells *in vivo* and *in vitro* (Figure 1). These features clearly distiguish the Recognins as a family of related antigens. Therefore, the Examiner's comments regarding the requirement of undue experimentation to find other Recognins is

unfounded, and absent some showing that there is reason to believe that all types of cancer do not produce the same Recognin antigen, this ground of rejection should be withdrawn.

The Examiner also states that it is unpredictable whether the antibodies produced upon administration of the 250,000 D protein would be the same as those produced upon exposure to the 10,000 D protein. However, as described in the prior art relied upon by the Examiner in making this rejection, the smaller 10,000 D protein was obtained by injecting the 250,000 D protein into rabbits, which produced antibody thereto. Then the 250,000 D protein was hydrolyzed to smaller peptides and it was demonstrated the only fragment of the 250,000 D protein that reacted with the antibody was malignin - all other peptide fragments gave negative results. Thus, it has been clearly shown that the 250,000 D precursor protein specifically produces anti-malignin antibody upon injection that has the same reactivity as the antibody produced by the 10,000 D malignin fragment of the precursor.

The Examiner states that the cytotoxicity of the anti-malignin antibodies has only been demonstrated <u>visually</u> in glioblastoma brain cancer and that this is an insufficient demonstration of the effectiveness of the claimed method and vaccine. However, Appellant is unaware of any antibody that has been demonstrated to actually lyse glioblastoma cells where the antigen is known. Visual evidence is classically relied upon in the field of immunology in showing cell lysis. Thus, Appellant's data is consistent with that which is accepted by those of ordinary skill in the art to demonstrate cytotoxicity of the antibody. Unless the Examiner is aware of other evidence which shows that this type of data is not reliable in respect to the Recognin antibody, this ground of rejection is improper and should be withdrawn.

The Examiner maintains that Appelant's *in vitro* studies are not sufficient to demonstrate that the adminsitration of Recognin would result in the treatment of cancer because the cytotoxicity measured *in vitro* cannot be extrapolated to the treatment of tumors *in vivo*, especially since the situation *in vivo* is more complex and unpredeictable. It is conceded that the treatment of any disease is multi-variate and complex. However, it is not a medical tenet that all factors that play a role in a particular disease state must be controlled in order to effectively treat the disease. Appellant is aware of no effective treatment of any disease that controls more than one or a few variables of the disease. For example, in the trdeatment of juvenile type diabetes mellitus, the level of insulin is a significant variable which is controlled by a treatment regimen involving injection of insulin. Such treatment permits the more normal utilization by the body of glucose and thus, reverses the pathology that results in ketosis, coma and early death, i.e., in the teens or early twenties as is commomly seen in untreated individuals. Nonetheless, injection of insulin does not result in the complete control of all the pathological variables in juvenile onset diabetes. Vascular complications, which result in blindness and other vascular disease symptoms frequently requiring amputation or resulting in early death 10 to 20 years sooner than the average human life span, still occur despite the control of insulin. However, provision of insulin to an individual suffering from juvenile onset diabetes is a medically accepted therapy that can extend the individual's life to a life span of 40 to 50 years.

Similarly, in the adult form of diabetes mellitus, insulin may not be needed, and diet and exercise alone may suffice to control diabetes, ketosis, coma and prevent early death. In some cases of adult diabetes, however, insulin is required. Thus, the

therapeutic effectiveness of treating with insulin, although this therapy controls only one variable in the pathology of the disease, cannot be denied.

The Examiner's requirement that all variables be accounted for in order to demonstrate that a treatment is effective in controlling a particular disease is inaccurate and not based on fact. One of ordinary skill in the art would not require, nor expect that all variables involved in a cancerous condition be controlled in order to provide an effective treatment of the cancer. Instead, intervention in the pathology of a significant variable is routinely accepted by those of ordinary skill in the art as effective treatment of disease. In this regard, Appellant has provided sufficient evidence that administration of Recognin benefits either the treatment or prevention of cancer. The evidence provided by Appellant includes the following:

- Recognins appear only when cells are in a malignant state as evidenced by:

1. the presence of malignin in malignant cells and absence thereof in normal cells;
2. the specificity of anti-malignin for malignant cells, regardless of tissue source and the failure of anti-malignin to interact with normal cells;
3. the presence of anti-malignin antibodies *in vivo*;
4. the ability to preferentially label malignant cells *in vivo* with anti-malignant antibody;

5. the increase in concentration of anti-malignin antibody in a patient's serum when a cell moves from the normal state, through a

borderline normal state, and into a frankly malignin state; and

6. the return to normal of the concentration of anti-malignin antibody in serum when malignant cells are either destroyed or removed.

- Anti-malignin antibody is the same regardless of whether malignin, Recognin-L or Recognin-M provides the antigenicity;

- Anti-malignin antiboby is cytotoxic/cytostatic to malignant cells only, at extremely low concentrations (fentomolar concentratons) per cancer cell, making this antibody the most potent antibody known in terms of cytotoxicity to cancer cells.

- Anti-malignin antibody increases in concentration in the serum with respect to the age of the individual, and thus the risk of cancer.

- In non-tumor bearing members of high risk families having a higher than normal frequency of cancer, antibody levels start at higher than normal levels, e.g., at the age of about twenty these individuals have a higher concentration of anti-malignin antibody than found in normal individuals of about age sixty. Moreover, the concentration of antibody continues to rise with age of the high risk family member.

- The concentration of anti-malignin antibody relates at $p < .001$ to survival of cancer patients; that is, the more anti-malignin antibody, the longer the survival time. This is a highly significant variable and the anti-malignin

antibody is the only antibody for which this relationship has been demonstrated in humans.

Accordingly, it is respectfully submitted that the evidence provided above and in Appellant's Brief clearly shows that the subject application provides an enabling disclosue of the method of treatment of cancer and vaccine to adequately teach one of ordinary skill in the art how to make and use the claimed invention.

For the reasons set forth herein, together with Appellant's Brief on Appeal, the final rejection by the Examiner should not be sustained.

Respectfully submitted,

Date February 27, 1996

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